

Applicants : John H. HEALEY and Gene R. DIRESTA
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Amendments to the Claims:

1-37. (canceled)

38. (Previously presented) A composition useful as local drug delivery system comprising:

(a) a polymeric bone-cement component in the form of particles, and

(b) an anti-resorptive agent in the form of particles,

wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution.

39. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is a bisphosphonate or a pharmaceutically acceptable salt or ester thereof.

40. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is pamidronate or pharmaceutically acceptable salt or ester thereof.

41. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is etidronate or a pharmaceutically acceptable salt or ester thereof.

42. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is alendronate or a pharmaceutically acceptable salt or ester thereof.

43. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is zoledronate or a pharmaceutically acceptable salt or ester thereof.

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44. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is gallium fluoride.
45. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is a cholesterol-lowering agent.
46. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is an estrogen-bisphosphonate conjugate.
47. (Previously presented) The composition of claim 38, wherein the bone-cement is an acrylic bone-cement or a hydroxyapatite bone-cement.
48. (Previously presented) The composition of claim 38, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is pamidronate or a pharmaceutically acceptable salt or ester thereof.
49. (Previously presented) The composition of claim 38, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is zoledronate, zoledronic acid, or a pharmaceutically acceptable salt or ester thereof.
50. (Previously presented) The composition of claim 38, wherein 65 to about 70 percent of the particles have an average diameter of about 25 microns.
51. (Previously presented) The composition of claim 38, wherein 30 to about 35 percent of the particles are about 13 to about 17 microns in diameter.

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52. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is present on the bone-cement's surface.
53. (Previously presented) The composition of claim 38, wherein the anti-resorptive agent is impregnated in the bone-cement.
54. (Previously presented) A composition comprising:
- (a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and
 - (b) an anti-resorptive amount of an anti-resorptive agent wherein the anti-resorptive agent is present in an amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from the living bone.
55. (Previously presented) The composition of claim 54, wherein the amount of the anti-resorptive agent is about 0.067 grams to about 6.67 grams per 40 grams of bone cement.
56. (Previously presented) The composition of claim 54, wherein the cement is an organic cement and the anti-resorptive agent is pamidronate in an amount from about 3% to 3.5% by weight of the composition.
57. (Previously presented) The composition of claim 54, wherein the amount of the anti-resorptive agent is about 0.67 micrograms to about 3.33 milligrams per 40 grams of bone-cement.

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58. (Previously presented) The composition of claim 54, wherein the amount of the anti-resorptive agent is about 1.34 micrograms to about 0.2 milligrams per 40 grams of bone-cement.
59. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is a bisphosphonate or a pharmaceutically acceptable salt or ester thereof.
60. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is pamidronate or a pharmaceutically acceptable salt or ester thereof.
61. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is etidronate or a pharmaceutically acceptable salt or ester thereof.
62. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is alendronate or a pharmaceutically acceptable salt or ester thereof.
63. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is zoledronate or a pharmaceutically acceptable salt or ester thereof.
64. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is gallium fluoride.
65. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is a cholesterol-lowering agent.

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66. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is an estrogen-bisphosphonate conjugate.
67. (Previously presented) The composition of claim 54, wherein the bone-cement is an acrylic bone-cement or hydroxyapatite bone-cement.
68. (Previously presented) The composition of claim 54, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is pamidronate or a pharmaceutically acceptable salt or ester thereof.
69. (Previously presented) The composition of claim 54, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is zoledronate, zoledronic acid, or a pharmaceutically acceptable salt or ester thereof.
70. (Previously presented) The composition of claim 54, wherein the anti-resorptive agent is present in an amount that is not toxic to osteoblast while toxic to osteoclasts.
71. (Previously presented) A composition comprising:
- (a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and
 - (b) an anti-resorptive agent selected from the group consisting of a salt of a Group IIIA element, a cholesterol-lowering agent, a chemotherapeutic agent-bisphosphonate conjugate, and an estrogen bisphosphonate conjugate.

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72. (Previously presented) A composition comprising: (a) a bone-cement selected from the group consisting of (1) a mixture comprising an acrylate monomer and a copolymer wherein the copolymer comprises (A) an acrylate or methylmethacrylate monomer and (B) an acrylonitrile, butadiene, styrene, vinyl chloride, vinylidene chloride, or vinyl acetate monomer; (2) an inorganic cement; and (3) a composite cement; and (b) an anti-resorptive amount of an anti-resorptive agent selected from the group consisting of a salt of a Group IIIA element; a cholesterol-lowering agent; an estrogen-bisphosphonate conjugate; and a bisphosphonate wherein the bisphosphonate is selected from the group consisting of pamidronate; alendronate; risedronate; ibandronate; zoledronate; olpadronate; icandronate; neridronate (6-amino-1-hydroxyexilidene-1, 1 bishphosphonate); dichloromethane bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutane-1, 1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazolyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyI-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; N-cycloheptylaminoethanebisphosphonic acid; S-(p-chlorophenyl) thiomethane-bisphosphonic acid; 4-amino-1-hydroxybutyliden-1, 1-bisphosphonic acid; (7-dihydro-1-pyrindine)methane bisphosphonic acid; (7-dihydro-1-pyrindine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyrindine)hydroxy-methanebisphosphonic acid; 2-(6-pyrilopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof.
73. (Previously presented) A composition comprising: (a) a bone-cement selected from the group consisting of (1) an

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organic cement, (2) an inorganic cement, and (3) a composite cement; and (b) a bisphosphonate selected from the group consisting of olpadronate; icandronate; neridronate; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazolyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyI-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; (7-dihydro-1-pyrindine)methane bisphosphonic acid; (7-dihydro-1-pyrindine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyrindine)hydroxymethanebisphosphonic acid; 2-(6-pyrolopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof.

74. (Previously presented) A composition comprising: (a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and (b) a bisphosphonate selected from the group consisting of dichloromethane bisphosphonic acid; N-cycloheptylamino-methanebisphosphonic acid; and S-(p-chlorophenyl) thio-methane-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof.

75. (Previously presented) A composition comprising: (a) a bone-cement selected from the group consisting of (1) and organic cement, (2) an inorganic cement, and (3) a composite cement; and (b) a bisphosphonate selected from the group consisting of 1-hydroxyethane-1,1-bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof.

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76. (Previously presented) A composition comprising: (a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and (b) a bisphosphonate selected from the group consisting of zoledronate, zoledronic acid, and pharmaceutically acceptable salts and esters thereof.

77. (Currently Amended) A composition ~~useful as~~for local drug delivery ~~system~~ comprising:

(a) a monomeric bone-cement component;

(ab) a polymeric bone-cement component in the form of particles, and

(bc) an amount of an anti-resorptive agent in the form of particles,

wherein the anti-resorptive agent is uniformly mixed with the polymeric bone-cement component first before the polymeric bone-cement component is mixed with the monomeric bone-cement component,

wherein the polymeric bone-cement component comprising the anti-resorptive agent is uniformly mixed with the monomeric bone-cement component to effect a polymerization reaction to obtain a polymerized bone-cement matrix,

wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution to provide for even distribution of the anti-resorptive particles throughout the polymerized bone-cement matrix after polymerization reaction, and to prevent the anti-

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resorptive agent from leaching out at different rates and ensure uniform drug delivery to tissue adjacent to the polymerized bone-cement matrix,

wherein the amount of anti-resorptive agents added to the polymeric bone-cement component does not weaken the bone-cement component or polymerized bone-cement matrix, or interfere with polymerization reaction of the bone-cement components,

wherein the polymerization of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agents, and

wherein the anti-resorptive amount of anti-resorptive agents is the amount of anti-resorptive agent, which is evenly distributed throughout the polymerized bone-cement matrix, sufficient to prevent the loosening of the polymerized bone-cement matrix from a living bone to which is it attached for an extended period of time.

78. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is a bisphosphonate or a pharmaceutically acceptable salt or ester thereof.
79. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is pamidronate or pharmaceutically acceptable salt or ester thereof.
80. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is etidronate or a pharmaceutically acceptable salt or ester thereof.

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81. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is alendronate or a pharmaceutically acceptable salt or ester thereof.
82. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is zoledronate or a pharmaceutically acceptable salt or ester thereof.
83. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is gallium fluoride.
84. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is a cholesterol-lowering agent.
85. (Previously presented) The composition of claim 77, wherein the anti-resorptive agent is an estrogen-bisphosphonate conjugate.
86. (Previously presented) The composition of claim 77, wherein the bone-cement is an acrylic bone-cement or a hydroxyapatite bone-cement.
87. (Previously presented) The composition of claim 77, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is pamidronate or a pharmaceutically acceptable salt or ester thereof.
88. (Previously presented) The composition of claim 77, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is zoledronate, zoledronic acid, or a pharmaceutically acceptable salt or ester thereof.
89. (Currently amended) The composition of claim 77, wherein 65 to about 70 percent of the polymeric bone-cement

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particles and the anti-resorptive agents have an average diameter of about 25 microns.

90. (Currently amended) The composition of claim 77, wherein 30 to about 35 percent of the polymeric bone cement particles and the anti-resorptive agents are about 13 to about 17 microns in diameter.

91. (Currently amended) The composition of claim 77, wherein the anti-resorptive agent is present on the outer surface of the polymerized bone-cement matrix,~~'s surface~~ or is uniformly distributed around the surface of the polymerized bone-cement matrix.

92. (Currently amended) The composition of claim 77, wherein the anti-resorptive agent is impregnated throughout the polymerized bone-cement matrix after polymerization reaction.

93. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) an anti-resorptive amount of an anti-resorptive agent,

wherein the anti-resorptive agent is present in an amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from the living bone;~~and~~

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wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component,

wherein the polymerization reaction of the components of the bone-cement does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agents is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

94. (Previously presented) The composition of claim 93, wherein the amount of the anti-resorptive agent is about 0.067 grams to about 6.67 grams per 40 grams of bone cement.
95. (Previously presented) The composition of claim 93, wherein the cement is an organic cement and the anti-resorptive agent is pamidronate in an amount from about 3% to 3.5% by weight of the composition.
96. (Previously presented) The composition of claim 93, wherein the amount of the anti-resorptive agent is about 0.67 micrograms to about 3.33 milligrams per 40 grams of bone-cement.
97. (Previously presented) The composition of claim 93, wherein the amount of the anti-resorptive agent is about 1.34 micrograms to about 0.2 milligrams per 40 grams of bone-cement.

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98. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is a bisphosphonate or a pharmaceutically acceptable salt or ester thereof.
99. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is pamidronate or a pharmaceutically acceptable sale or ester thereof.
100. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is etidronate or a pharmaceutically acceptable sale or ester thereof.
101. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is alendronate or a pharmaceutically acceptable sale or ester thereof.
102. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is zoledronate or a pharmaceutically acceptable salt or ester thereof.
103. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is gallium fluoride.
104. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is a cholesterol-lowering agent.
105. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is an estrogen-bisphosphonate conjugate.
106. (Previously presented) The composition of claim 93, wherein the bone-cement is an acrylic bone-cement or hydroxyapatite bone-cement.

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107. (Previously presented) The composition of claim 93, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is pamidronate or a pharmaceutically acceptable salt or ester thereof.

108. (Previously presented) The composition of claim 93, wherein the bone-cement is polymethylmethacrylate and the anti-resorptive agent is zoledronate, zoledronic acid, or a pharmaceutically acceptable salt or ester thereof.

109. (Previously presented) The composition of claim 93, wherein the anti-resorptive agent is present in an amount that is not toxic to osteoblast while toxic to osteoclasts.

110. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) an anti-resorptive agent selected from the group consisting of a salt of a Group IIIA element, a cholesterol-lowering agent, a chemotherapeutic agent-bisphosphonate conjugate, and an estrogen bisphosphonate conjugate,

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component, -

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wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

111. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

(a) a bone-cement selected from the group consisting of
(1) a mixture comprising an acrylate monomer and a copolymer wherein the copolymer comprises (A) an acrylate or methylmethacrylate monomer and (B) an acrylonitrile, butadiene, styrene, vinyl chloride, vinylidene chloride, or vinyl acetate monomer; (2) an inorganic cement; and
(3) a composite cement; and

(b) an anti-resorptive amount of an anti-resorptive agent selected from the group consisting of a salt of a Group IIIA element; a cholesterol-lowering agent; an estrogen-bisphosphonate conjugate; and a bisphosphonate wherein the bisphosphonate is selected from the group consisting of pamidronate; alendronate; risedronate; ibandronate; zoledronate; olpadronate; icandronate; neridronate (6-amino-1-hydroxyexilidene-1, 1 bishphosphonate); dichloromethane bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 4-amino-1-

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hydroxybutane-1, 1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazolyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyI-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrollidino)-1-hydroxypropane-1,1-bisphosphonic acid; N-cycloheptylamino-methane-bisphosphonic acid; S-(p-chlorophenyl) thiomethane-bisphosphonic acid; 4-amino-1-hydroxybutyliden-1, 1-bisphosphonic acid; (7-dihydro-1-pyrindine)methane bisphosphonic acid; (7-dihydro-1-pyrindine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyrindine)hydroxy-methane-bisphosphonic acid; 2-(6-pyrilopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof, and

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component, -

wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

112. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

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(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) a bisphosphonate selected from the group consisting of olpadronate; icandronate; neridronate; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazolyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyl-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; (7-dihydro-1-pyridine)methane bisphosphonic acid; (7-dihydro-1-pyridine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyridine)hydroxy-methanebisphosphonic acid; 2-(6-pyrollopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof, and

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component,

wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

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113. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) a bisphosphonate selected from the group consisting of dichloromethane bisphosphonic acid; N-cycloheptylaminoethanebisphosphonic acid; and S-(p-chlorophenyl) thiomethane-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof, and

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component,

wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

114. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

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(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

(b) a bisphosphonate selected from the group consisting of 1-hydroxyethane-1,1-bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; and pharmaceutically acceptable salts and esters thereof, and

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component,

wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

115. (Currently amended) A composition for arresting the process of aseptic loosening attributed to osteoclasts comprising:

(a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and

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(b) a bisphosphonate selected from the group consisting of zoledronate, zoledronic acid, and pharmaceutically acceptable salts and esters thereof, and

wherein the amount of anti-resorptive agent does not weaken the bone-cement component or interfere with polymerization reaction of the bone-cement component,

wherein the polymerization reaction of the bone cement components does not chemically interfere with or inactivate the anti-resorptive agent, and

wherein the anti-resorptive agent is uniformly distributed throughout the polymerized bone-cement by first mixing the polymeric bone-cement component of the bone-cement with anti-resorptive agent, which has the same or similar particle size distribution as the polymeric bone-cement component of the bone-cement, prior to polymerization reaction.

116. (Currently amended) The composition of claim 1—38 produced by the steps of: (a) mixing a polymer component with an anti-resorptive amount of an anti-resorptive agent to form a mixture; and (b) adding a liquid monomer component to the mixture.

117. (Previously presented) The composition of claim 77 produced by the steps of: (a) mixing a polymer component with an anti-resorptive amount of an anti-resorptive agent to form a mixture; and (b) adding a liquid monomer component to the mixture.

118-121. (Canceled)

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122. (New) The composition of claim 77, wherein the amount of the anti-resorptive agent is about 1 microgram to about 11 grams per 60 grams of bone cement.
123. (New) The composition of claim 77, wherein the amount of the anti-resorptive agent is about 0.1 grams to about 10 grams per 60 grams of bone cement.
124. (New) The composition of claim 77, wherein the amount of the anti-resorptive agent is about 0.5 grams per 60 grams of bone cement.
125. (New) The composition of claim 77, wherein the amount of the anti-resorptive agent is about 1 microgram to about 5 milligrams per 60 grams of bone cement.